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(54) Title: INCLUSION COMPOUNDS OF NIMESULIDE WITH CYCLODEXTRINS

(57) Abstract

Inclusion compounds of nimesulide with cyclodextrins, in the molar ratio of nimesulide to cyclodextrin comprised between 1:0.5 and 1:15, which possess high solubility and are more rapidly absorbed and/or better tolerated than nimesulide itself.

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INCLUSION COMPOUNDS OF NIMESULIDE WITH CYCLODEXTRINS

The present invention relates to new compounds obtained by complexation of nimesulide with cyclodextrins, to the processes for their preparation and to pharmaceutical compositions containing them.

Nimesulide is the International Non-proprietary name for 4-nitro-2-phenoxy-methansulfonanilide, patented in USA (US Pat. 3,480,597). Nimesulide is a non-steroidal anti-inflammatory drug useful in the treatment of inflammatory and pain states, such as chronic rheumatoid arthritis or osteoarthritis, otorhinolaryngological diseases, soft tissues, oral cavity inflammation and postoperative pain states. Nimesulide presents the usual side-effects associated with non-steroidal antiinflammatory drugs. Furthermore it is known that nimesulide has a very poor water solubility, and this gives rise to well-known difficulties, e.g. preparation of suitable pharmaceutical compositions, poor rate of release and therefore a poor and erratic bioavailability.

It has been now found, and this is the object of the present invention, that nimesulide can be advantageously complexed by inclusion into an unsubstituted or substituted α-, β- or γ-cyclodextrin or a hydrate thereof.

The inclusion compound so obtained is useful as analgesic and antiinflammatory drug and possesses good water solubility. it is absorbed in a more efficent and rapid way, and it shows a virtually improved gastric tolerability.

The efficacy of the new inclusion compound has been tested by known pharmacological methods.

Cyclodextrins are cyclic oligosaccharides consisting of at least six glucopyranose units which are joined together by α-1,4-glucosidic bonds. Although, cyclodextrins with up to 12 glucose residues are known, only three homologs have been studied extensively: α-, β-, and γ-cyclodextrins consisting of 6,7 and 8 glucose residues respectively. The cyclodextrin molecules are of cylindrical shape, having a central axial cavity. The outer surface of these molecules is hydrophilic, while the internal cavity is of apolar character. This feature allows other molecules ("guest molecules") or part of them, which are less polar than water and are of suitable dimensions, to penetrate in the lipophilic cavity of the inner part of the cylindric cyclodextrin molecule, forming thereby the inclusion compound.

Suitable cyclodextrins which may be used according to the present invention are unsubstituted or substituted α-, β- or γ-cyclodextrins or hydrates thereof. Examples of substitued cyclodextrins include surphur-containing cyclodextrins, nitrogen-containing cyclodextrins, methylated cyclodextrins, hydroxypropyl--β-cyclodextrins.

Conveniently a single unsubstituted cyclodextrin is employed according to the present invention, particularly preferred is β-cyclodextrin.

For the preparation of the inclusion compounds of nimesulide with a cyclodextrin in a molar ratio comprised between 1 : 0.5 and 1 : 15, preferably 1 : 1 the following known methods are available:

a) the solutions of cyclodextrin in water and of nimesulide in a suitable organic solvent are strirred vigorously and the obtained complex is separated by filtration;

b) nimesulide and cyclodextrin are dissolved under stirring in a water-ammonia solution at a temperature from 0° to 100° C, preferably at room temperature. The desired compound is then obtained by freeze-drying or atomization;

c) a mixture of nimesulide and cyclodextrin in water is stirred for several days and the complex is obtained by evaporation under reduced pressure.

The following examples illustrate better the present invention, but they are not to be in any way considered limitative of the scope of the invention itself:

Example 1

A solution of nimesulide (0.5 g, 1.62 mmoles) in methylene chloride (15 ml) was added to a solution of β-cyclodextrin (1.84 g. 1.62 mmoles) in water (250 ml). After one night shaking at room temperature, the precipitate was collected by filtration and dried under vacuo at 40° C.

Example 2

A mixture of nimesulide (0.31 g, 1 mmoles) and β-cyclodextrin (1.13 g, 1 mmoles) in water (160 ml) was stirred at 60° C for 8 days. The solution then cooled at room temperature, evaporated to dryness and the residue was dried in vacuo at 40° C.

Example 3

Nimesulide (3 g, 9.73 mmoles) and β-cyclodextrin (11.05 g, 9.73 mmoles) were added under stirring in water (650 ml containing 2.5 ml of aqueous 30% ammonium hydroxide). The mixture was stirred one night at room temperature and the resulting solution was freeze-dried. The residue was treated with ethyl acetate, filtered and dried in vacuo at 40° C.

Example 4

Nimesulide (31 g, 0.1 moles) and β-cyclodextrin (283 g, 0.25 moles) were suspended in water (6500 ml) and a solution of aqueous 30 % ammonium hydroxide (30 ml) was added at room temperature. After one night the solution was dried by using a Uniglatt laboratory spray-dryer to give a granulate corresponding to the title complex.

The inclusion compound so obtained was characterized as follows:

1. Quantitative determination of nimesulide complexed by β-cyclodextrin.

   The quantity of nimesulide included in the complex with β-cyclodextrin is calculated by High Pressure Liquid Chromatography (HPLC) whose sperimental conditions are reported as follows:

   - Mobile phase : phosphate buffer 0.002 M pH 6.88: acetonitrile in the ratio 70 : 30
   - Flow rate : 1 ml/min.
   - Temperature : 40° C
   - Column : spheric RPs 5 µm (Hewlett-Packard)
   - λ detection : 400 nm
   - nimesulide ritention time: 4 min ca.

2. Differential Scanning Calorimetry (D.S.C.)

   Figure 1 shows the thermograms concerning nimesulide (trace a), β-cyclodextrin (trace b), physical mixture of both (trace c) and inclusion compound (trace d).

Nimesulide melts at 149° C and does not show any decomposition up to 240° C. β-cyclodextrin shows an endothermic event between 60° to 140°C correspondig to the elimination of water.

The trace of the physical mixture shows the thermal characteristics of both nimesulide and β-cyclodextrin.

The trace of the inclusion compound nimesulide-β-cyclodextrin, after the initial loss of weight at a temperature below 140° C attributable to the absorbed moisture, does not show any other thermic event up to 240° C. Therefore, the disappearance of the melting peak at 149° C of nimesulide shows that the inclusion compound has take place.

3. Infrared spectroscopy

IR spectra of nimesulide (a), of β-cyclodextrin (b), of 1 : 1 (mol : mol) physical mixture (c) and of the inclusion compound (d) are shown in the figure 2. Comparing the spectrum of the inclusion compound with that of the physical mixture, there are evident modifications in the bands around 1520 cm^{-1}, due to the asymmetric stretching of nitro group, and especially in the region 1300 - 1200 cm^{-1}, giving proof of the significant differences existing between the inclusion compound and the physical mixture, according to the conclusions drawn from the differential scanning calorimetry results.

Bioavailability and pharmacokinetic

Plasma kinetics were carried out in dog after oral administration of equivalent dosages of nimesulide and inclusion compound nimesulide -β-cyclodextrin according to a crossover scheme.

Four male Beagle of body weight between 12.8 and 13.9 kg, fasted for at least 17 hours, were orally administered the following preparations:

A) nimesulide at the dose of 10 mg/kg

B) inclusion compound nimesulide -β-cyclodextrin (molar ratio 1 : 1) at the dose of 46.84 mg/Kg, corresponding to 10 mg/kg of nimesulide.

The preparations were administered in gelatine capsule after a "wash-out" period of 10 days.

The blood samples from dogs were collected in eparinized tubes after 1, 2, 3, 4, 5, 6, 8, 24, 28, 32, 48 and 52 hours from the administration of the two preparations. The relative plasma samples were obtained by centrifugation for 15 minutes at 3000 rpm.

The plasma levels of nimesulide were determined by HPLC with UV detection according to the following procedure: aliquots of plasma up to 2.5 ml were adjusted to 3.5 ml with distilled water and acidified with 1.0 ml of N hydrochloric acid and poured on to a glass column (18 mm i.d. 220 mm of lenght) containing 15 ml of Extralat® Merck. After 15 minutes nimesulide was eluted with two aliquotes of 7.5 ml of dichloromethane containing 5% of methanol. The eluate was evaporated to dryness under reduced pressure and the residue was taken up with 200 µl of 2.5 µg/ml solution of butilhydroxyanisole as internal standard. A suitable amount was therefore injected into a column by using the following chromatographic conditions:

- Column RPCa, 5 µm, 250 x 3 mm i.d. Supelco;
- Mobile phase : acetonitrile + water containing 80 mg/l of EDTA in the ratio V/V 37.5 and 62.5 respectively;
- Flow rate : 1.0 ml/min.
- λ of detection: 230 nm

The obtained results are reported in table 1.

The parameters of AUC, C_{max} and T_{max} were calculated by the plasma levels of nimesulide using a computer fitting system with TOP FIT package and the results were statistically evaluated by the ANOVA TWO WAYS procedure.

The results of the kinetic parameters are reported in the table 2 and are statistically highly significative.

From the above reported results it can be concluded that the inclusion compound nimesulide-β -ciclodextrin increases significatively the bioavailability and the maximum plasma concentration (C_{max}) of nimesulide.

TABLE I Plasma levels of Nimesulide in the dog after oral administration of equivalent dosages of Nimesulide (10mg/Kg.) (A) and nimesulide-β-cyclodextrin inclusion compound (B)

PREPARATION	Dogs No.	means ± S.E.	Nimesulide plasma levels (μg/ml.) hours after administration											
			1	2	3	4	5	6	8	24	28	32	48	52
A	4	$\bar{X}$ ±	2.735	7.439	10.855	13.045	12.687	12.125	9.235	1.490	1.182	0.802	0.166	0.136
		S.E.	0.820	0.579	0.929	2.071	2.580	2.519	1.426	0.572	0.461	0.335	0.112	0.104
B	4	$\bar{X}$ ±	11.040	22.130	25.277	26.060	23.817	22.890	19.447	2.937	1.460	0.992	0.156	0.111
		S.E.	2.265	1.552	1.417	2.445	1.887	1.779	2.028	1.253	0.379	0.280	0.070	0.050

TABLE 2 Kinetic parameters

Preparation	dogs No.	Means ± S.E.	AUC (0→∞) µg.h/ml	C_{max} µg/ml	T_{Cmax} h
A	4	X ± S.E.	165.359 38.817	12.112 1.733	4.4 0.5
B	4	X ± E.S.	320.750 37.988	25.630 1.384	3.6 0.4

According to a further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient, nimesulide complexed by inclusion into cyclodextrins in the above defined ratios, in association with one or more pharmaceutical carriers, excipients or diluents.

For the pharmaceutical administration nimesulide complexed by inclusion into cyclodextrin may be incorporated into conventional pharmaceutical compositions in either solid or liquid form. The compositions may be presented, for example, in a suitable form for oral, rectal, parenteral administration or for topic use. Preferred forms include, for example, capsules, tablets, coated tablets, granules, ampoules, suppositories, oral drops, syrup, emulsion, gel, ointment and sustained release compositions.

The inclusion compound nimesulide-cyclodextrin may be formulated, with the excipients or carrier conventionally used in the pharmaceutical compositions such as, for example, talc, arabic gum, lactose, gelatine, magnesium stearate, corn starch, aqueous or non-aqueous vehicles, polyvinylpirrolidone, semisynthetic glicerides of fatty acids, sorbitol, glycerol vaseline, hydroxyethylcellulose, propylene glycol, citric acid, sodium citrate, flavouring, sweeteners, binders and disgregating agents.

The compositions are advantageously formulated in dosage unit; each dosage unit being adapted to supply a single dose of the active ingredient. Each dosage unit may conveniently contain from 5 to 300 mg, preferably from 20 to 150 mg of the active ingredient.

The following non-limitative examples illustrate the pharmaceutical compositions according to the present invention:

Example 5

Tablets (wet granulation)

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 50 mg of nimesulide)	240	mg
- hydroxypropylmethylcellulose	70	"
- microcrystalline cellulose	150	"
- colloidal silica	5	"
- magnesium stearate	5	"
	470	mg

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 100 mg of nimesulide)	480	mg
- hydroxypropylmethylcellulose	120	"
- microcrystalline cellulose	220	"
- colloidal silica	10	"
- magnesium stearate	10	"
	840	"

Method of preparation: the binder solution consisting of hydroxypropylmethylcellulose was used for the granulation of nimesulide and β-cyclodextrin, previously mixed with microcrystalline cellulose. After suitable drying the granulate so obtained was classified and mixed with colloidal silica and with magnesiun stearate. The composition was therefore pressed in order to obtain tablets containing 50 and 100 mg of nimesulide

Example 6

Tablets (direct compression)

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to mg 50 of nimesulide)	240	mg
- lactose	40	"
- calcium phosphate	60	"
- magnesium stearate	2	"
- colloidal silica	3	"
	345	mg

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 100 mg of nimesulide)	480	mg
- lactose	80	"
- calcium phosphate	120	"
- magnesiun stearate	4	"
- colloidal silica	6	"
	690	mg

Method of preparation: nimesulide in the form of inclusion compound with β-cyclodextrin was diluted progressively with lactose and calciun phosphate. To the mixture so obtained magnesiun stearate and colloidal silice were added. After a suitable mixing the composition was pressed in order to obtain tablets containing each 50 and 100 mg of nimesulide respectively.

Example 7

Capsules

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 50 mg of nimesulide)	240	mg
- hydroxypropylmethylcellulose	80	"
- magnesium stearate	10	"
	330	mg

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 100 mg of nimesulide)	480	mg
- hydroxypropylmethylcellulose	160	"
- magnesium stearate	15	"
- colloidal silica	5	"
	660	mg

Method of preparation: nimesulide in the form of inclusion compound with β-cyclodextrin was suitably diluted with the excipients and filled into gelatine capsule. Each capsule contains 50 and 100 mg of nimesulide respectively.

Example 8

Granules

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 50 mg of nimesulide)	240	mg
- sorbitol	2710	"
- aspartame	15	"
- raspberry flavour	35	"
	3000	"

Method of preparation: nimesulide in the form of inclusion compound with β-cyclodextrin was progressively diluted with sorbitol. After having mixed aspartame and flavor agent were added. Therefore, the mixture in the form of powder so obtained was filled into sachets. Each sachet contains 50 mg of nimesulide.

Example 9

Monodose containers

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 50 mg of nimesulide)	240	mg
- mannitol	500	"
- raspberry flavour	40	"
- sodium saccharinate	5	"
- phosphates	5	"
	785	mg
- Deionized water	19625	"

Method of preparation: mannitol was dissolved in a pH 7.1 buffered solution and then nimesulide in the form of inclusion compound with β-cyclodextrin was added under slight stirring at room temperature. The raspberry flavour and colouring agent were then added. The solution was filtered and filled into vials and then freeze-dried. Each vial contains 50 mg of nimesulide.

Example 10

Suppositories

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 50 mg of nimesulide)	240	mg
-semisynthetic glycerides of fatty acids	1260	"
	1500	mg

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 100 mg of nimesulide)	480	mg
- semisynthetic glycerides of fatty acid	1520	"
	2000	mg

Method of preparation: the suppository mass was melted and nimesulide in the form of inclusion compound with β-cyclodextrin was added under continuous and constant stirring. Then. it was cooled at a proper temperature until the mass so obtained was poured into performed moulds for suppositories. After cooling suppositories containing 50 or 100 mg of nimesulide were obtained.

Example 11

Oral drops

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 50 mg of nimesulide)	240	mg
- sodium saccharinate	40	"
- propylene glycol	400	"
- flavour	5	"
- demineralized water	515	"
	1200	mg

Method of preparation: sodium saccharinate was dissolved in water under slight stirring, then nimesulide in the form of inclusion compound with β-cyclodextrin was added. The resulting solution was diluted by dropping propylene glycol and lastly the flavour was added. The solution so obtained was distributed in 30 ml polyethylene bottle and dosed by a proper dropper in order to obtain 20 drops (1 ml) for a dosage of 50 mg of nimesulide.

Example 12

Syrup		
- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 50 mg of nimesulide)	2400	mg
- hydroxyethylcellulose	200	"
- 70% sorbitol solution	50000	"
- glycerol	12750	"
- benzoic acid	200	"
- tartaric acid	100	"
- raspberry flavour	330	"
- deionized water	50580	"
	≅ 100.0	mg

Method of preparation: hydroxyethylcellulose was dispersed in the proper amount of the warm water until a solution was obtained. Then benzoic acid, tartaric acid, glycerol and then nimesulide in the form of inclusion compound with β-cyclodextrin were added under slight stirring. To the so obtained solution sorbitol solution was added, and lastly the flavour. Each spoon (≅ 10 ml) contains 50 mg of nimesulide.

Example 13

Ointment

- Nimesulide -β-cyclodextrin (1 : 1) (equivalent to 2,5 g. of nimesulide)	11.7	g.
- vaseline-oil	12.3	"
- white vaseline	76.0	"
	100.0	g.

Method of preparation: nimesulide in the form of inclusion compound with β-cyclodextrin was dispersed in the vaseline oil at the temperature between 45-50° C. At this stage the white vaseline, previously heated at the same temperature. was added. The mixing stage was completed under vacuun by a turbo-mixer. Then the mass was cooled reducing also the stirring intensity. At the end the ointment was put into aluminium tubes (100 g/tube).

CLAIMS

1. Compounds obtained by complexation of nimesulide with an unsubstituted or substituted α-, β- or γ-cyclodextrin, or a hydrate thereof in a molar ratio comprised between 1 : 0.5 and 1 : 15 of nimesulide and cyclodextrin respectively.

2. Compounds according to claim 1 wherein the molar ratio of nimesulide/cyclodextrin is 1 : 1.

3. Compounds according to claims 1 and 2 wherein the cyclodextrin is β-cyclodextrin.

4. Process for the preparation of the compounds according to claims 1 - 3, characterized in that an aqueous solution of cyclodextrin is interacted with an organic solution of nimesulide from which the inclusion product is isolated by filtration.

5. Process for the preparation of the compounds according to claims 1 - 3, characterized in that nimesulide and cyclodextrin are interacted at room temperature and under stirring in a water-ammonia solution.

6. Process according to claim 5, characterized in that the inclusion compound is isolated by freeze-drying of the solution.

7. Process according to claim 5, characterized in that the inclusion compound is isolated by atomization of the solution.

8. Pharmaceutical compositions having analgesic and antiinflammatory activity containing, as active ingredient, at least a compound according to claims 1 - 3.

9. Pharmaceutical compositions according to claim 8 containing from 20 to 150 mg of active ingredient for dosage unit.

10. Use of the compounds according to claims 1-3 for the manufacturing of a medicament for the treatment of inflammatory and pain states.

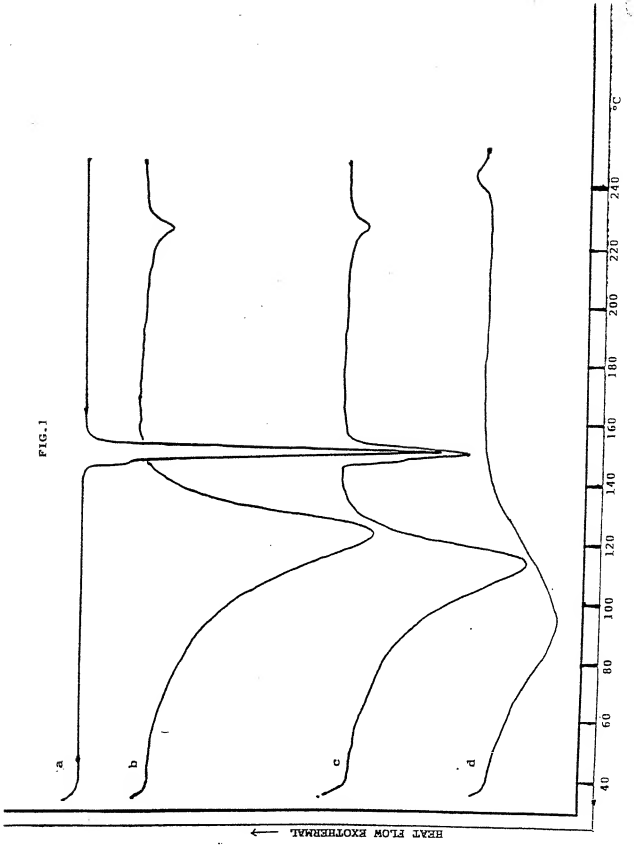
HEAT FLOW EXOTHERMAL
a
b
c
d
40
60
80
100
120
140
160
180
200
220
240
°C

FIG.1

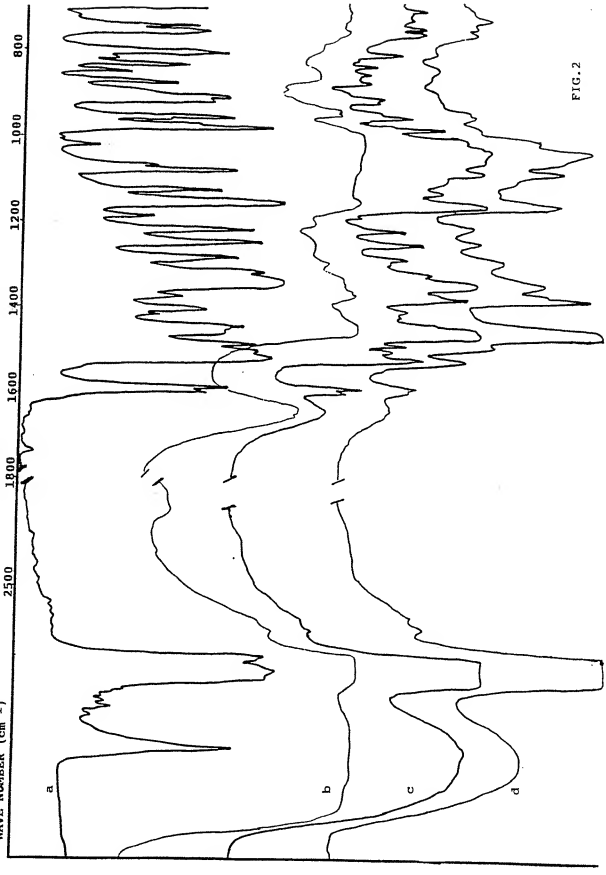

FIG. 2

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 47/48 A 61 K 31/63

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
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Y	CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 26, no. 4, April 1978, pages 1162-1167, Pharmaceutical Society of Japan, K. UEKAMA et al.: "Inclusion complexation of beta-cyclodextrin with some sulfonamides in aqueous solution", see whole article	1-10
A	FR,A,2190460 (RIKER LAB.) 1 February 1974, see claims 1,9 (cited in the application)	1-10

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13-08-1991	27. 09. 91
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	miss T. MORTENSEN

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. IT 9100043 SA 47528

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 18/09/91
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(54) Title: A WATERSOLUBLE NIMESULIDE ADDUCT ALSO FOR INJECTABLE USE

(57) Abstract

The present invention relates to a nimesulide adduct with an amino sugar, in particular N–methylglucamine, and to pharmaceutical compositions containing the same. The pharmaceutical composition may contain cyclodextrins and/or surfactants, such as Cremophor EL or Tween 80. Said adduct has a very good water solubility and can be used also in pharmaceutical formulation for injectable use.

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A WATERSOLUBLE NIMESULIDE ADDUCT ALSO FOR INJECTABLE USE

The present invention relates to a new nimesulide adduct with an amino sugar and to pharmaceutical formulations containing the same.

Nimesulide, the chemical name of which is N- (4-nitro-2-phenoxyphenyl)-methanesulfonamide, is a well-known, non-steroidal, anti-inflammatory and anti pyretic drug useful in all the affections involving pain or an inflammatory state. However, it is known that nimesulide has very poor water solubility, and this makes its use difficult in aqueous formulations for oral or injectable use. Furthermore this poor water solubility negatively affects the drug bioavailability.

WO 91/17774 and WO 94/02177 disclose inclusion compounds of nimesulide with cyclodextrins. By using said inclusion compounds, the nimesulide solubility increases to 0.61 mg/ml, which is about 20 times the solubility of pure crystalline nimesulide.

WO 95/34533 discloses the nimesulide salt with L-lysine. By using this salt, the nimesulide solubility is 5.42 mg/ml. Said solubility increases to 30.16 mg/ml in the presence of a γ-cyclodextrin at a concentration of 200 mM.

The present invention provides a nimesulide adduct with an amino sugar which already per se has a very good water solubility even without cyclodextrins. The nimesulide water solubility, obtained by using the adduct of the present invention, is more than 160 mg nimesulide/ml. This excellent solubility makes the nimesulide granular formulation in single dose sachets easy and rapid to dissolve in water at the time of use, without leaving any deposit as in the case of the analogous formulations on the market. This property enables the patient always to take the correct dose of nimesulide.

It is possible furthermore to dissolve the usual dose of the drug (100mg) in a few millilitres of water thus allowing obtaining clear injectable formulations, which remain stable, at a temperature from 25° to 40°C, for long periods.

Another remarkable advantage of the adducts according to the present invention is an improved bioavailability which allows a lower dosage in comparison with the formulations presently on the market.

The present invention refers to an adduct between nimesulide and an amino sugar, wherein the term "adduct," means the addition product between nimesulide and the amino sugar. In particular the adduct may be a salt or a complex.

The molar ratio between nimesulide and amino sugar may vary from 1:1 to 1:10, preferably from 1:1 to 1:6.

The amino sugar may be, for example, glucamine, glucosamine, condrosamine and the derivatives thereof, such as the N-alkyl derivatives, wherein the alkyl group has 1 to 4 carbon atoms. The N-methyl derivatives are particularly preferred. Both the enantiomeric forms and their racemic mixture are comprised in the scope of the present invention. N- methyl-glucamine is the most preferred.

The nimesulide adduct with N-methylglucamine obtained according the method reported in the following Example 1 has a ratio nimesulide: N-methylglucamine of 1:4.5.

Fig.1 shows the I.R. spectrum of nimesulide.

Fig.2 shows the I.R. spectrum of N-methylglucamine.

Fig.3 shows the I.R. spectrum of the physical mixture of nimesulide and N-methylglucamine.

Fig.4 shows the I.R. spectrum of the nimesulide-N-methylglucamine adduct according to the invention.

Another object of the present invention are also pharmaceutical formulations containing the nimesulide adduct with an amino sugar. Said formulations may optionally contain pharmaceutically acceptable excipients and/or carriers, such as, for example, talc, gum arabic, lactose, mannitol, gelatine, magnesium stearate, starch, aqueous or non-aqueous vehicles, polyvinylpyrrolidone, semisynthetic glicerydes of fatty acids, sorbitol, glycerol, vaseline, hydroxyethylcellulose, propylene glycol, hydroxypropylethylcellulose, microcrystalline cellulose, citric acid, sodium citrate, colloidal silica, calcium phosphate, flavouring agents, sweeteners, binders, and disgregating agents.

The pharmaceutical formulation of the adduct according to the present invention are advantageously formulated in dosage units; each dosage unit containing from 5 to 300 mg, preferably from 20 to 150 mg nimesulide.

The pharmaceutical formulations according to the present invention may further contain a cyclodextrin wherein the cyclodextrin may be an α-, β-, γ-cyclodextrin, a derivative or a mixture thereof.

The pharmaceutical formulations of the adduct according the present invention may also contain a surfactant, preferably an anionic surfactant.

A suitable anionic surfactant may be, for example, the condensation product of ethylene oxide with a fatty acid such as a polyoxyethylene laurate, stearate or oleate as sold under the trademark Mirj; or the condensation product of ethylene oxide with a vegetal oil, for example castor oil or a derivative thereof, as sold under the trademarks Cremophor, Micelliphor, Texophor, Emulphor (or Mugolfen); or the condensation product of ethylene oxide with a long chain aliphatic alcohol, for example polyoxyethylene cetylether, laurylether, stearylether or oleylether, such as the products sold under the trademark Brij; or a condensation product of the ethylene oxide with a partial ester obtained from a fatty acid and a hexitol anhydride, such as polyoxyethylene sorbitan monolaurate, monopalmitate, monostearate or monooleate, as sold under the trademark Tween; or a polyoxyethylene-polyoxypropylene copolymer, as sold under the trademark Pluronic.

Particularly suitable products are Tween 20, 40, 60, 80; Mirj 52 or 53; Brij 35; Pluronic F68; Emulphor (or Mugolfen) EL 620 or 719; Texophor D40 or D80; Cremophor EL, RH40 or RH60 or Micelliphor. Particularly preferred are Cremophor EL and Tween 80.

The adduct according to the present invention may be incorporated into conventional pharmaceutical composition in either solid or liquid form. Suitable forms for oral administration may be, for example, tablets, capsules, granules, oral drops, and syrup; for parenteral administration, injectable solutions; for rectal administration, suppositories; for topic administration, creams, ointments, pastes, eye drops, sprays.

Formulations absorbable through a mucous tissue, such as powders to be sprayed into the nose, are comprised in the scope of the present invention. Formulations for transdermic administration, such as transdermic patches, are also comprised in the scope of the present invention.

A further object of the present invention is a solid mixture of nimesulide with an amino sugar. By adding water, said mixture forms the adduct according to the present invention.

The adduct according to the present invention is obtained by a process comprising the following steps:

1. suspending nimesulide in water under vigorous stirring,
2. adding the amino sugar while stirring until the nimesulide is completely dissolved,

The solution obtained is clear.

The solution is brought to the volume desired by adding water. The solution pH must be preferably be 10.2 ± 0.5. Then the solution is filtered through a special membrane with a porosity of 0.22 μm.

The obtained solution can be dried by methods well known to the persons skilled in the art such as evaporation by heating under vacuum, spray-drying, or freeze-drying.

A yellowish powder with a humidity of 1% ± 0.5 is thus obtained.

If in the manufacturing process the equipment is sanitized and the raw materials are apyrogenic, a product suitable for parenteral use is obtained.

EXAMPLE 1

PREPARATION OF THE NIMESULIDE-N-METHYLGLUCAMINE ADDUCT

640 ml distilled water are placed into a small dissolver. 26.7 g nimesulide are suspended under vigorous stirring and 79.095 g N-methylglucamine are slowly added. The suspension is kept under vigorous stirring until the nimesulide is completely dissolved. The solution is brought to the final volume of 800 ml by adding distilled water. The pH which must be 10.2 ± 0.5, is checked. Possible adjustments must be carried out by adding nimesulide or N- methylglucamine.

The thus obtained solution is filtered through a membrane having a porosity of 0.22 μm. The yellow-orange coloured solution is then freeze-dried using the following parameters:

-freezing for 5 hours at –40°C

-heating to +45°C with a gradient of 0.15°C/min at a vacuum of 0.2 mm Hg.

-final heating to +45°C for 8-10 h at a vacuum of less than 0.2 mm Hg. The residual humidity is 1 ± 0.5 %.

EXAMPLE 2

VIAL/AMPOULE FORMULATION: 100 mg/3ml

Nimesulide-N-methylglucamine adduct	385 mg
Water for injections	q.s. to 3 ml

EXAMPLE 3

VIAL/AMPOULE FORMULATION: 100 mg/5ml

Nimesulide-N-methylglucamine adduct	385 mg
Absolute ethyl alcohol	350 mg
Cremophor El	1800 mg
Water for injections	q.s. to 5 ml

The pH of the final solution was adjusted to 8,5-9 by adding glacial acetic acid or N- methylglucamine.

EXAMPLE 4

FORMULATIONS IN UNIT DOSAGE SACHETS: 100 mg/sachet

Nimesulide-N-methylglucamine adduct	385 mg
Sucrose	2.8 g
Orange flavour	85 mg
Maltodextrins	23 mg

The above reported amounts of nimesulide-N-methylglucamine adduct, sucrose (containing maltodextrins) and orange flavour are placed into a suitable powder mixer. All these raw materials have been previously sieved.

Mixing is continued for about 30 min or at any rate until the mixture is homogeneous.

The so obtained granulate is divided into sachets of a coupled material of aluminium-paper-polyether having an average weight of 3.293 g.

EXAMPLE 5

FORMULATION IN TABLETS: 100 mg /tablet

Nimesulide-N-methylglucamine adduct	385 mg
Avicel	100 mg
Magnesium stearate	15 mg
Talcum	10 mg
Sodium carboxymethylcellulose	40 mg

The above reported amounts of nimesulide-N-methylglucamine adduct, Avicel, magnesium stearate, talcum and sodium carboxymethylcellulose are placed into a suitable powder mixer. All these raw materials must have been previously sieved.

Mixing is continued for about 30 min or at any rate until the mixture is homogeneous.

The thus obtained granulate is compressed into tablets having an average weight of 550 mg.

CLAIMS

1. An adduct of nimesulide with an amino sugar.
2. An adduct according to claim 1 wherein the amino sugar is selected from the group consisting of glucamine, glucosamine, condrosamine and a N-(C_{1-4}) alkyl-derivative thereof.
3. An adduct according to claim 2 wherein the amino sugar is N-methyl-glucamine.
4. An adduct according to claims 1 to 3 wherein the molar ratio of nimesulide to amino sugar may vary from 1:1 to 1:10.
5. An adduct according to claim 3 wherein the molar ratio of nimesulide to N-methylglucamine is 1:4.5.
6. A pharmaceutical formulation containing the adduct according to claims 1 to 5 and optionally one or more pharmaceutically acceptable excipients and/or carriers.
7. A pharmaceutical formulation according to claim 6 further comprising a cyclodextrin.
8. A pharmaceutical formulation according to claim 7 wherein the cyclodextrin is an α-, β- or γ-cyclodextrin or a derivative or a mixture thereof.
9. A pharmaceutical formulation according to any one of the claims 6 to 8 further containing a surfactant.
10. A pharmaceutical formulation according to claim 9 wherein the surfactant is Cremophor EL or Tween 80.
11. A pharmaceutical formulation in solid form containing a mixture of nimesulide and of an amino sugar.
12. An adduct according to claims 1 to 5 for therapeutic use.
13. Use of an adduct according to claims 1 to 5 for manufacturing a medicament for the treatment of inflammatory affections.

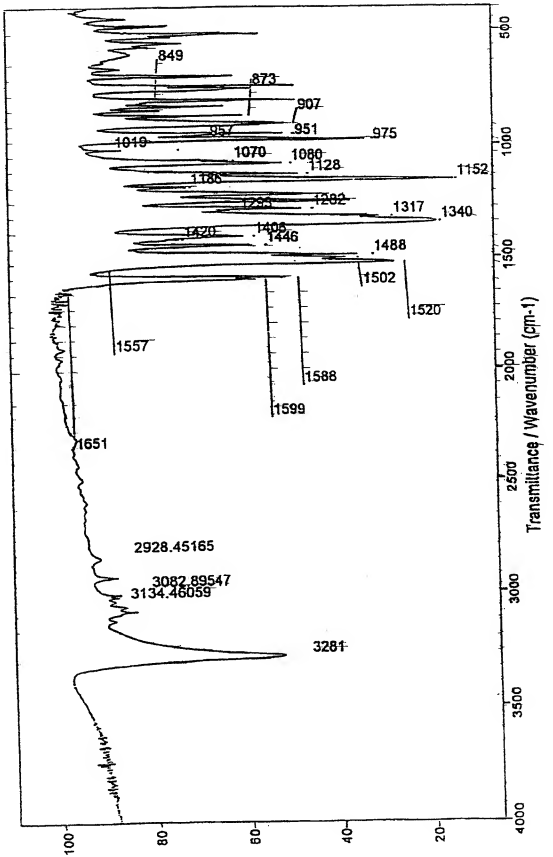
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FIG. 1

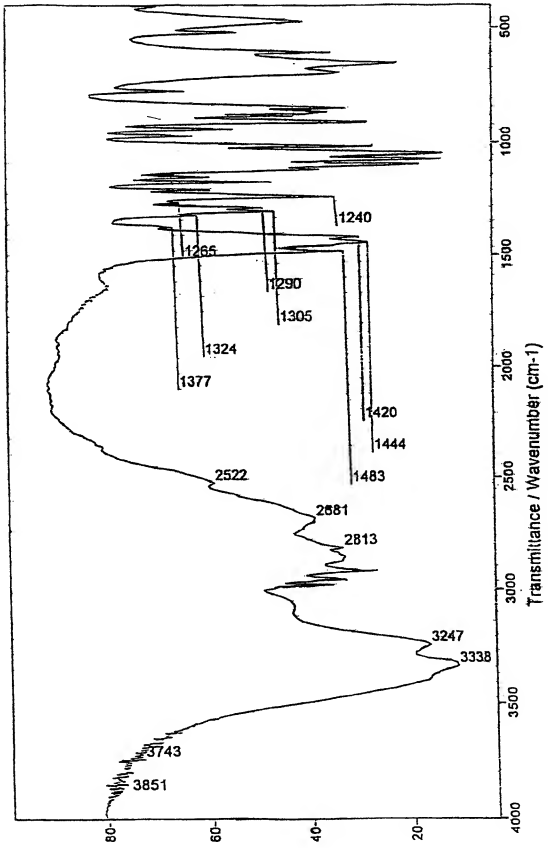
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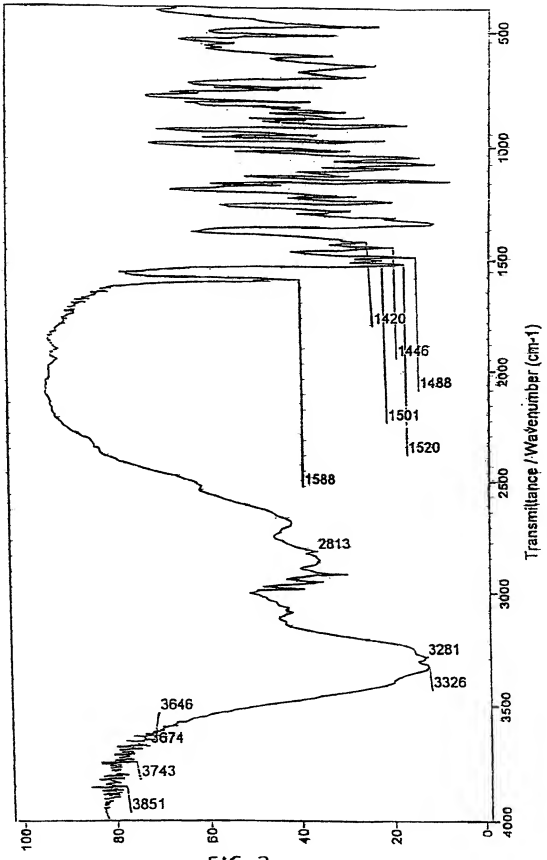
FIG. 2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Transmittance / Wavenumber (cm-1)
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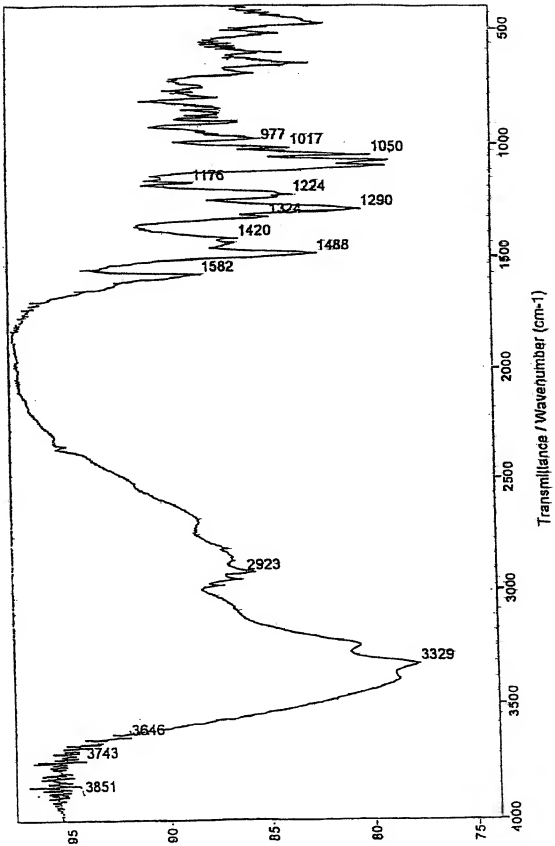
FIG. 3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Transmittance / Wavenumber (cm-1)
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FIG. 4

INTERNATIONAL SEARCH REPORT

Ii ational Application No
PCT/IB 99/00086

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/08 C07C215/10 C08B37/16 A61K31/63 A61K47/18
A61K47/26 A61K9/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C08B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 17774 A (BOEHRINGER INGELHEIM ITALIA) 28 November 1991 cited in the application see page 1 - page 4 ---	1,6
A	WO 95 34533 A (EUROPHARMACEUTICALS) 21 December 1995 cited in the application see page 2; claims 1,5,16 ---	1,6
A	US 4 482 554 A (U. GEBHARDT, ET AL.) 13 November 1984 see column 1 ------	1,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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